

2. The following reaction is used: Under the action of dicyclohexyl carbodiimide (DCC), to let the carbobenzyloxy protecting alanine (Z-Ala) react with (HOSu) at 20~25°C for 5 hours, after filtering the dicyclohexylurea, proceed the synthesis in aqueous solution of sodium bicarbonate with non-protected Gln, the product is reduced by hydrogenation in methyl alcohol to remove the protective group, and then the alanylglutamine is obtained. (Literature: Katoh, T. Kurauchi, M. Eur. Pat. 311,057, 12 Apr. 1989) The reagents used in this method are expensive, it is difficult to remove the products of DCC after reaction, and the process of production is more complicated.

3. The following reaction is used: phosgene (COCl_2) reacts with Ala to form mixed anhydride, then reacts with Gln in water, pH of the solution is maintained at 10.2, at last, remove protective group in acid solution, and then the alanylglutamine is obtained. (Literature: Frerst, P. Pfaendetr, P. Ger. Offen. DE 3206,784. 01 Sep. 1983) The reaction procedure of this method is less, but phosgene is a virulent gas, the reaction is hard to complete, and it is more harmful to human body.

4. Acyl chloride is formed by activating the chiral reagent chloropropionic acid with SOCl_2 , and then reacts with Gln in aqueous solution of NaOH, pH of the solution is maintained at 10. The product is dichloropropionylglutamine, it reacts with liquid ammonia under a certain pressure, then the alanylglutamine is obtained. (Literature: Takahiro Sano, Toru Sugaya, Process Research and Development of 1-Alanul-1-glutamine, a Component of Parenteral Nutrition, Organic Process Research and Development. 2000,4,147-152). The raw material of this reaction is chiral reagent, it is higher in cost, in the synthesis procedure of acylchloride, reaction temperature is higher, and there are too many side reactions. So that when it is used in production, the production cost may be too expensive.

The object of this invention is to provide a synthesis method of alanylglutamine which is cheap in raw materials, simple in synthesis technique, low in production cost,

high in productivity and advantageous to environment protection.

Procedure of the synthesis method of Alanylgutamine is provided below:

- 1) 10 mmol of N-terminal protected alanine (I), 10~30 mmol, preferably 15~20 mmol of triphenylphosphine and 10~30 mmol, preferably 15~20 mmol of hexachloroethane react in organic solvent (II) for 0.3~3 hours, preferably for 1.5~2 hours, at reaction temperature $-5\sim 30^{\circ}\text{C}$, preferably at $0\sim 10^{\circ}\text{C}$, to form the active ester;
- 2) Let the reaction mixture containing the active ester as mentioned in step 1 to react with 10~30 mmol of glutamine in a mixed liquid containing organic solvent (III) and aqueous solution of inorganic base (IV), (due to there is organic solvent existed in step 1), the volume ratio of III and IV is 0~4, when the property of organic solvent (II) used in step 1 coincides with that of organic solvent (III), then no more organic solvent might be used in step 2, at this time, the volume ratio of III and IV is 0, preferably 0.5~2, the reaction temperature is $-5\sim 30^{\circ}\text{C}$, preferably $5\sim 10^{\circ}\text{C}$, and pH of the solution is

into a liquid mixture containing 30 mmol of glutamine, 20 ml of water and 20 ml of cyclohexane. While reacting, regulates pH to 12 with sodium hydroxide, the reaction temperature is 25°C, the reaction time after dropping is 30 min. And then regulate pH to 1.5 by acidifying it with dilute nitric acid. The aqueous phase, after concentrated, reacts with 20% hydrogen bromide/glacial acetic acid at room temperature for 5 hours. As the reaction is finished, drop in 50 ml of ether, solids deposit, the product L-Ala-L-Gln is obtained with a yield of 50% by recrystallizing with methanol-water.

Example 4

In a round bottom flask, add in 10 mmol of N-(O,O-dimethyl) phosphoalanine, 20 mmol of triphenylphosphine and 30 mmol of hexachloroethane respectively, and then add in 20 ml of toluene. After reacting at 5°C for 1 hour, add it into a liquid mixture containing 10 mmol of glutamine, 20 ml of water and 5 ml of ethanol. While reacting, regulate pH to 9.5 with sodium carbonate, the reaction temperature is 5°C, the reaction time is 10 min. And then regulate pH to 1.0 by acidifying it with phosphoric acid. The aqueous phase, after concentrated, reacts with trifluoroacetic acid at room temperature for 15 hours. As the reaction is finished, add in 50 ml of ether, solids deposit, the product L-Ala-L-Gln with a yield of 40% is obtained by recrystallizing the solids with methanol-water.

Example 5

Dissolve 20 mmol of triphenylphosphine with 10 ml of methylhydrofuran, drop it into a mixed system composed of 10 mmol of N-(O,O-diethyl) phosphoalanine, 30 mmol of hexachloroethane and 10 ml of tetrahydrofuran. After reacting at -5°C for 2 hours, add it into a liquid mixture containing 10 mmol of glutamine, 20 ml of water and 20 ml of ethanol. While reacting, regulate pH to 9.5 with 10 mmol of sodium hydroxide and then with sodium bicarbonate successively, the reaction temperature is -5°C, the reaction time after dropping is 2 hours. And then acidify it to regulate pH=3 with concentrated hydrochloric acid. The aqueous phase, after concentrated, reacts with saturated hydrogen chloride/glacial acetic acid at room temperature for 5 hours. As

the reaction is finished, adding 50 ml of ether, solids deposit, the product L-Ala-L-Gln is obtained with a yield of 35% by recrystallizing the solids with ethanol-water.

Example 6

Dissolve 30 mmol of hexaethane with 20 ml of dichloromethane, drop it into a mixed system composed of 10 mmol of N-(O,O-diethyl) phosphoalanine, 30 mmol of triphenylphosphine and 10 ml of dichloromethane. After reacting at 0°C for 40 min., drop it into a liquid mixture containing 30 mmol of glutamine, 20 ml of water and 10 ml of cyclohexane. While reacting, regulate pH to 13 with potassium hydroxide, the reaction temperature is 20°C, the reaction time after dropping is 30 min. And then acidify it to regulate pH=1.5 with dilute nitric acid. The aqueous phase, after concentrated, react with trifluoroacetic acid at room temperature for 10 hours. As the reaction is finished, add in 50 ml of ether, solids deposit, the product L-Ala-L-Gln is obtained with a yield of 60% by recrystallizing the solids with 1,4-dioxane-water.